

Solvent Effects by Means of Averaged Solvent Electrostatic Potentials: Coupled Method

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ABSTRACT: In this article we propose a mean field theory that permits the calculation of solvent effects in a direct way by combining quantum mechanics and molecular dynamics simulations. Because of the reduced number of necessary quantum calculations, it is possible to get the same level of theory used for molecules *in vacuo*. The electronic structure of the solute in solution and the solvent structure around it are optimized in a self-consistent way. The main characteristics of the proposed method are high-level quantum calculations in the representation of the solute, a detailed description of the solvent structure through molecular dynamics calculation, inclusion of the mutual polarization of the solute and solvent molecules, and an accurate description of the solute–solvent interaction energy. As an application of the model we studied the polarization of quantum mechanically treated water and methanol molecules in the liquid phase. © 2000 John Wiley & Sons, Inc. *J Comput Chem* 21: 705–715, 2000

Keywords: quantum mechanics method; molecular mechanics method; mean field approximation; water; methanol

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Introduction

One of the challenges of present computational chemistry is to get the same level of calculation and accuracy for molecules in solution that has been achieved for molecules *in vacuo*. The path to this goal is complicated because of several factors, for instance, the huge number of degrees of freedom of liquids: the great number of solvent configurations that are necessarily included to make the calculations statistically significant, the great number of molecules involved in the description of the bulk solvent polarization, and the almost complete absence of symmetry that would permit one to simplify the problem. Hence, and to make the problem tractable, it is generally necessary to introduce approximations in the description of the solute, the solvent, or both.

One of the most fruitful approaches in the study of solvent effects limits the explicit quantum-mechanical treatment to a small part of the system, the solute, while the remaining part of the system, the solvent, is represented classically.¹ Even in this case the computational task can be enormous. For instance, in quantum and molecular mechanics (QM/MM) methods, which combine QM in the description of the solute and MM for the solvent, it is necessary to perform a quantum calculation for each chosen solvent configuration. Because of this, it generally is necessary to restrict the level of the quantum calculation and to employ semiempirical methods² or, less often, density functional theory³ (DFT) or Hartree-Fock⁴ (HF) with reduced basis sets. It seems clear that, while waiting for new computational strategies, if we need to increase the quality of the quantum calculations, we have to reduce their number. This can be done by using the mean field approximation (MFA) in which the perturbation due to the solvent effect is introduced in an averaged way. More specifically, the quantity that is introduced into the solute molecular Hamiltonian is the averaged value of the solvent potential. In the past this approximation was mainly used with very simplified descriptions of the solvent, such as those provided by the dielectric continuum⁵ or Langevin dipole models.⁶ A more detailed description of the solvent was used by Ten-no et al.⁷ who describe the solvent through atom-atom radial distribution functions obtained via an extended version of the interaction site method. Less attention was paid, however, to the use of the MFA in conjunction with simulation calculations of liquids, although its theoretical bases are well known.⁸

In this respect, we refer to the articles of Sesé et al.⁹ in which the radial distribution functions that represent the solvent are obtained from molecular dynamics (MD) calculations.¹⁰

In previous articles (hereafter referred to as article I¹¹ and article II¹²) we proposed a mean field theory for the study of solvent effects that combines QM and MD calculations in the same spirit as in QM/MM methods. In our model the solvent structure around the solute is obtained in a standard MD calculation. The averaged solvent electrostatic potential (ASEP) can then be calculated from MD data. This potential enters as a perturbation in the molecular Hamiltonian of the solute. It is clear that in this way the solute's energy and wave function are influenced by the result of the simulation process. However, the MD process is not affected by the result of the quantum calculation, so we referred to this version of the model as "noncoupled." We developed two versions of the model: one with nonpolarizable (article I) and one with polarizable (article II) solvents. In both cases it was shown that the proposed mean field theory adequately reproduces the energy and electric properties of solutes in solution. The mutual polarization of the solute and solvent molecules is a very important aspect of the solvation problem. The continuum and Langevin dipole methods generally include this contribution. However, to date, only a few QM/MM calculations have included the effect of this component.¹³ The reason is clear: a proper consideration of this effect can only be achieved through a self-consistent process. This means that, in the best of the cases, three or four quantum calculations are needed to reach convergence, resulting in a notable increase in computational difficulty. Because of this, approximate, non-self-consistent procedures have generally been used.

In this present article we extend the above model to make the process self-consistent and thus simultaneously optimize the electronic structure of the solute in solution and the solvent structure around it. To this end, it is enough to introduce the solute charge distribution obtained from the solute wave function in the potential energy function used in the MD calculation and to repeat the procedure until convergence in the charges is reached. We refer to this second model as "coupled."

In the following section we show how to extend the previous model to take into account the coupling between the solute electron distribution and the solvent structure. Then we study different factors that affect the polarization of molecules in solution. As an application of the model we study two

liquid systems: water and methanol. Both are characterized by a high degree of short-range structure and strong electrostatic interactions, so they constitute a severe test for any theory of solvent effects. Furthermore, the water system has been abundant the subject of studies¹⁴ so that we may compare and contrast our result with those obtained using other methodologies. The final section presents the main conclusions.

Method

The solvent effect theory involving coupling between a quantum and a classical system has been widely discussed by various authors.^{1–4,15} Here we summarize for clarity the main points of our implementation of the methodology. We begin by reviewing the procedure for obtaining the ASEP. A more complete description of the same can be found elsewhere.^{11,12}

Our Hamiltonian model is partitioned in the usual way as

$$H = H_{\text{QM}} + H_{\text{MM}} + H_{\text{QM-MM}} \quad (1)$$

with terms that correspond to the quantum part, H_{QM} , and the classical part, H_{MM} , and to the interaction between them, $H_{\text{QM-MM}}$. In our case the quantum part is only formed by the solute molecule. The classical part is formed by the set of discrete solvent molecules inside a spherical cavity of radius a centered on the solute molecule and a dielectric continuum surrounding the solute and the discrete solvent molecules. The radius of the spherical cavity is taken as half the side of the simulation box. The dielectric continuum corrects the error associated with the finite size of the cavity that contains the discrete molecules. Key features of the model we use to represent the solute–solvent system are shown in Figure 1.

The energy and state function of the solvated solute molecule are obtained by solving the effective Schrödinger equation:

$$(H_{\text{QM}} + H_{\text{QM-MM}})|\Psi\rangle = E|\Psi\rangle. \quad (2)$$

The interaction term, $H_{\text{QM-MM}}$, takes the following form in our model:

$$H_{\text{QM/MM}} = \sum_i \frac{q_i \hat{\rho}}{r_{ij}}, \quad (3)$$

where $\hat{\rho}$ is the charge density operator associated to the solute molecule and $\{q_i\}$ is a set of charges that reproduce the values of the ASEP. The charges are obtained in two steps. First, we include the

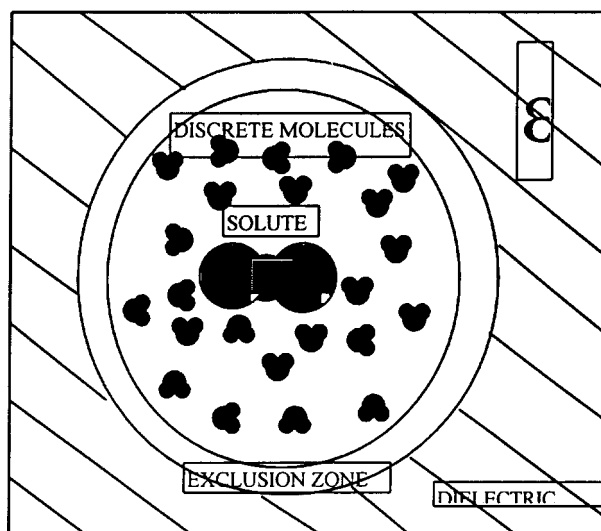


FIGURE 1. Key features of the model including the solute molecule, the discrete solvent molecules, and the dielectric continuum. The exclusion layer is also shown.

charges belonging to solvent molecules that, in any of the MD configurations, lie within the first solvation shell. The value of any charge is then divided by the number of solvent configurations included in the calculation of the ASEP. Second, a set of charges is obtained by a least squares fit to the values of the ASEP originated by the solvent molecules lying beyond the first solvation shell.¹⁶ The total number of charges introduced into the perturbation Hamiltonian is about 5000.

In the noncoupled model the process is completed by introducing the perturbation attributable to the charges into the molecular Hamiltonian and solving the associated Schrödinger equation. In this case only one quantum calculation is necessary to obtain the solvent effect, independent of the number of solvent configurations considered. In the coupled method additional calculations are necessary.

The scheme of the coupled method is shown in Figure 2. The procedure begins by performing one quantum calculation for the solute molecule in the gas phase. The *in vacuo* solute charge distribution is then used as input in the MD calculation. Once the structure of the solvent around the solute molecule is obtained from the MD data, the ASEP is determined and introduced into the molecular Hamiltonian of the solute. The electronic wave function of the solute now in solution can be obtained by solving the associated effective Schrödinger equation. A new solute charge distribution can be calculated from the solute wave function and used again as input in a new MD calculation. This process

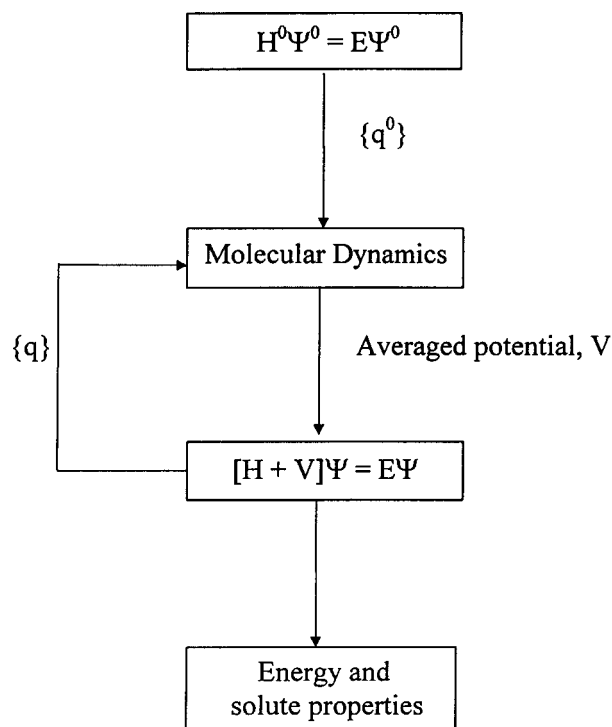


FIGURE 2. The coupled model scheme. In the partially coupled model the charge distribution $\{q\}$ is only used in the description of the solute molecule during the MD calculation. In the completely coupled model (valid only for pure liquids) $\{q\}$ is also used to represent the solvent molecules.

is repeated until convergence in the solute charges is achieved. During the self-consistent process the solute charge distribution changes at each step of the cycle; however, the charge distribution of the solvent molecules used in the MD calculation always remains the same. We refer to this version of the model as partially coupled (PC). The solute charges used in the MD calculation were obtained by fitting the molecular electrostatic potential of the solute molecule in the presence of the solvent perturbation in the standard way. The CHELP program was used.¹⁷

The PC version can be used in the study both of solutions and of pure liquids. In the latter case there exists the possibility of following a second strategy. Now the solute and solvent molecules are identical. Obviously, the charge distribution of each molecule depends on its particular surroundings, but given that we are using a mean field theory we can consider that the average electric field that each molecule feels is the same for all of them; hence, we can suppose that all the molecules in the liquid have identical average charge distributions. This

means that we can use the charge distribution obtained for the solute molecule—quantum mechanically treated water (henceforth termed “quantum water” for brevity) for instance—to represent all the molecules (quantum and classical water) in the MD calculation. We remark that in this version the solvent molecules are represented by the atomic charges obtained in the quantum calculation of the solute molecule. This solvent charge distribution is used in the MD and in the calculation of the ASEP. We referred to this version of the model as completely coupled (CC). In this version the solvent charge distribution (which is a replica of the solute charge distribution) changes at each cycle (i.e., it is polarized), and hence we have to include an additional term that accounts for the energy spent in polarizing the solvent molecules. One of the main characteristics of the CC version is that the electrostatic interaction potential used in the MD calculation is determined during the calculation. The only part of the potential that has to be previously known is the Lennard–Jones (LJ) term.

Given that we suppose that solute and solvent molecules are identical, the distortion energy or energy spent in polarizing every molecule can be calculated as

$$\Delta E^{\text{pol}} = \langle \Psi | H_{\text{QM}} | \Psi \rangle - \langle \Psi^0 | H_{\text{QM}} | \Psi^0 \rangle. \quad (4)$$

The total potential energy of the system reads

$$E = \frac{1}{2}N(E^{\text{int}} + E^{\text{LJ}}) + N\Delta E^{\text{pol}} \quad (5)$$

with the solute–solvent interaction energy defined as

$$E^{\text{int}} = \langle \Psi | H_{\text{QM-MM}} | \Psi \rangle \quad (6)$$

and where N is the total number of molecules included in the simulation and E^{LJ} is LJ energy per molecule. In obtaining eq. (5) we supposed that on average all the molecules have the same interaction energy. For pure liquids the quantity that can be compared with the experimental result is the vaporization energy or averaged total potential energy, $\langle E \rangle$, that can be easily calculated by dividing eq. (5) by N :

$$\langle E \rangle = E/N = \frac{1}{2}(E^{\text{int}} + E^{\text{LJ}}) + \Delta E^{\text{pol}}. \quad (7)$$

In the PC version the solute and solvent molecules carry different charge distributions and have different distortion energies. Because of this, expression (5) is not yet adequate. In this case we follow the work of Wei and Salahub^{3a} and Tu and Laaksonen^{4d} and use the internal energy defined as

$$\langle E \rangle = \frac{1}{2}(E^{\text{int}} + E^{\text{LJ}} + \Delta E^{\text{pol}}) \quad (8)$$

as an estimate of the interaction between the QM molecule and the MM molecules.

In short, the main characteristics of our method are high-level quantum calculations in the representation of the solute, a detailed description of the solvent structure through MD calculations, inclusion of the mutual polarization of the solute and solvent molecules, and an accurate description (without multipolar expansions) of the solute–solvent interaction energy.

Technical Details

In this article the model described above was applied to the study of two pure liquids: water and methanol. The basis set used in both cases was the aug-cc-pDZV from Dunning and colleagues¹⁸ (hereafter B4). This basis set yields values for the *in vacuo* dipole moment and polarizability close to the experimental values (see Table I). The wave functions and energies were calculated at HF level, and second-order Møller–Plesset (MP2) perturbation theory corrections to the energy (PTE) and density matrix (PTDE) were added when indicated. All the quantum calculations were done using the Gaussian 94 package.¹⁹

In the water system and to test the response of the method to changes in the description of the wave function, three additional basis sets were considered. These basis provide values for the dipole moment (1.95, 1.97, and 1.96 D) close to the experimental value (1.85 D) and furthermore cover a wide range of values of polarizabilities. Our simplest basis set, B1, is the standard 6-21G(d,p)²⁰ split valence basis set. This basis was then improved as B2 with the addition of diffuse functions on the oxygen atom, 6-21+G(d,p). Finally, the B3 basis set has two diffuse functions on the oxygen atom and one on the hydrogen atoms. The diffuse functions, designed for the study of electrical properties, were taken from Zeiss et al.²¹

All the MD calculations were done using the program MOLDY.²² In the PC version the solvent

molecules were simulated by the TIP3P²³ model at fixed intramolecular geometry. The LJ parameters of the solute molecule were the TIP3P values, but the charges were obtained from a quantum calculation. In the CC version all the molecules had charges obtained from a quantum calculation and the LJ parameters were taken from the TIP3P model. This approximation (unchanged LJ parameters + modified charges) has been fruitfully used in several polarizable MD calculations.^{14p–r} In fact, it is generally assumed that these parameters depend only on the hybridization of the QM atom and are fully transferable from one system to another.¹ The geometry of the quantum water molecule was the same as used for the rest of the molecules in the MD calculation (i.e., the TIP3P geometry). Periodic boundary conditions were applied and spherical cutoffs were used to truncate the water–water interactions at 9 Å. A time step of 0.5 fs was used. The electrostatic interaction was calculated with the Ewald method. The first simulation was run for 150,000 time steps (50,000 equilibration, 100,000 production). The solute and solvent coordinates were dumped at every 20 steps for further analysis. The grid defined inside the solute molecule rotates and translates with the solute molecule in such a way that all the solvent coordinates can be referred to a reference system centered on the solute mass center with the coordinate axis lying along the principal axes of inertia of the solute. Next the ASEP was calculated and introduced into the solute Hamiltonian. A new set of charges for the solute molecule was obtained and a new MD calculation was performed (50,000 time steps for equilibration and 100,000 steps for results). The process continued until self-convergence in the solute charges. The criterion of convergence was fixed at 0.001 au. The radius of the cavity that contains the discrete molecules (see Fig. 1) was taken as 9 Å and the extra exclusion radius as 2 Å, although the results were found to have hardly any dependence on this latter parameter. In fact, the contribution of the continuum to the solute–solvent interaction energy was less than 0.3 kcal/mol, which represents

TABLE I.
In Vacuo Dipole Moment and Polarizabilities of Water Molecule.

	B1	B2	B3	B4	B4-PTDE	Exp.
μ^0	1.95	1.97	1.96	2.00	1.87	1.87
α^0	4.6	6.4	8.5	8.2	9.2	9.7

Dipole moments are in debyes; Polarizabilities are in atomic units. For a description of basis sets B1, B2, B3, and B4 see the text.

TABLE II. In-Solution Dipole Moment (D) and Solute–Solvent Quantum Interaction Energy (kcal/mol) for Water–Water System as Function of Number of Cycles of Self-Consistent Process.

Basis set	Step	0	1	2	3	4
B1	μ	1.95	2.21	2.28	2.30	
	ΔE	—	−13.0	−15.8	−17.00	
B2	μ	1.97	2.35	2.48	2.50	
	ΔE	—	−14.3	−19.2	−19.8	
B3	μ	1.96	2.42	2.59	2.69	2.71
	ΔE	—	−14.5	−20.2	−23.7	−24.2

The calculations were performed with the partially coupled method at the Hartree–Fock level.

less than 2%. This result indicates that the number of discrete solvent molecules included in the calculation is high enough. The calculations were performed on an IBM RISC 6000-550.

Results and Discussion

WATER

We begin by studying the convergence of the PC model. Table II shows the evolution of the solute dipole moment and solute–solvent interaction energy with the step number of the self-consistency process in the water–water system. Convergence in the charges or dipole moment of the solute is reached in about three to five steps, depending on the basis set, the number of cycles necessarily increasing with the size of the basis sets. The convergence of the CC version for the B1 and B2 basis sets is similar to that obtained with the PC model.

The convergence in the self-consistent process is shown graphically in Figure 3. As was expected, the dipole moment value increases with the step number until convergence is achieved with fluctuation around a mean value. The fluctuations in the induced dipole moment are very small. The variation between two consecutive steps is 0.3 D at the beginning but only 0.01 D at the end of the process. Convergence in the solute–solvent interaction energy is also reached in the same number of steps, although in this case the fluctuations are larger. The solute–solvent interaction energy is much more sensitive to small variations in the solvent structure than is the induced dipole moment.

We now describe the results of the different versions of the method for three basic magnitudes: the induced dipole moment, the interaction energy, and the solute–solvent radial distribution functions.

Figure 4 represents the induced dipole moment, $\Delta\mu$, as a function of the solute polarizability. The behavior is almost linear. The induced dipole moments are very sensitive to the nature of the basis sets. Note that although the three basis sets yield almost the same value for the *in vacuo* dipole moment, the induced dipole moments are very different as a consequence of the different description of the solute polarizability that the three basis sets provide. This shows how cautious one must be in interpreting results of solvent effects obtained with basis sets of low or medium quality. The $\Delta\mu$ values obtained with the PC version are 0.35, 0.53, 0.75, and 0.73 D for basis sets B1, B2, B3, and B4, respectively. The CC version yields slightly larger

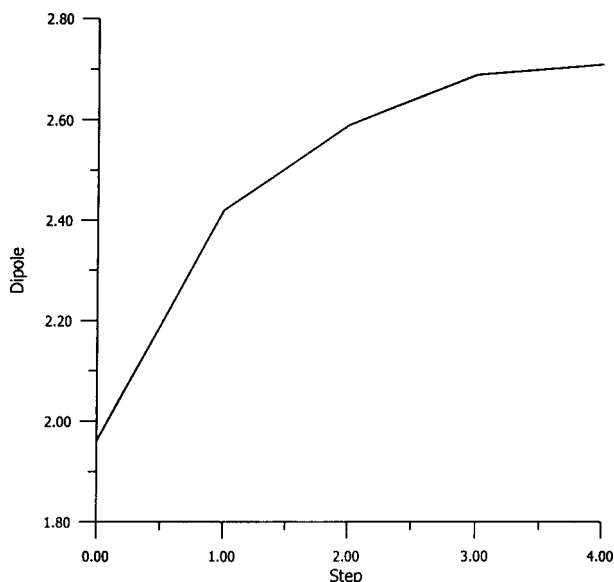


FIGURE 3. The variation of the solute dipole moment as a function of the number of cycles of the self-consistent process.

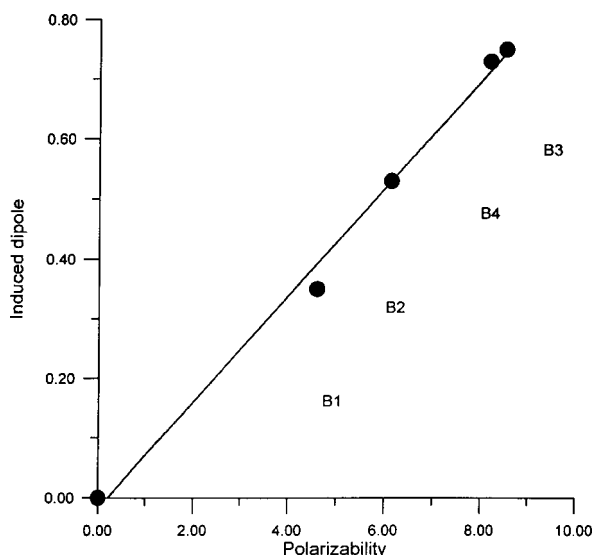


FIGURE 4. The variation of the induced dipole moment with the calculated values of the water molecule polarizability.

values. The inclusion of electron correlations (PTDE calculations) increases the induced dipole moment (0.81 D). The results obtained with the best basis sets, B3 and B4, compare well with the experimental value^{24, 25} (0.75 D) and with the values obtained by other workers. Thus, Jansen et al.^{14m} used a noncoupled model and CISD calculations to obtain 0.79 D, and Tuñón et al.^{3b} found a value of 0.61 D with a coupled Monte Carlo/DFT calculation but with a basis set of poorer quality. Tu and Laaksonen^{4d} found 0.65 D with a coupled HF/MM and with a basis of quality similar to our B3. In an *ab initio* water study Laaksonen et al.^{14l} obtained an induced dipole moment of 0.8 D employing a Carr–Parrinello type method.

The same behavior (strong dependence on the basis set) is shown by the solute–solvent interaction

energy (see Tables III, IV). As expected, ΔE increases with the solute polarizability. The CC method permits quantum polarization of the solvent molecules and hence yields larger values for the interaction energy, E^{int} , than the PC method. The lowest values are obtained with the B1 basis set. This basis set clearly underestimates the polarizability, 4.61 au,³ but yields a value for the in-solution dipole moment that agrees with the TIP3P dipole moment of about 2.3 D. The classical solute–solvent interaction energy as obtained from the MD calculations is -20.9 kcal/mol, which also agrees with the TIP3P value. However, the more precise quantum solute–solvent interaction energies (Table II), which include the solute polarization energy, are clearly smaller at only -16.5 or -17.0 kcal/mol, depending on whether the CC or PC version is used. It is remarkable that in order to reproduce the dipole value of the TIP3P model we have to employ a basis set whose polarizability is only one-half of the experimental value. The reason is that TIP3P and other effective pair potentials are generally adjusted to reproduce the experimental heat of vaporization; however, as we saw above, the classically calculated solute–solvent interaction energies are overestimated. Because of this and to bring the theoretical value into line with the experimental one, these classical models have to use charge distributions that give clearly underestimated values for the in-solution dipole moment.

As we already indicated, the quantity that can be compared with the experimental values is $\langle E \rangle$. The PC method yields internal energies that are systematically greater than the values obtained with the CC version, despite the interaction energies and dipole moments being larger with this latter method. The reason is clear: in the PC method the solvent molecules are represented at the TIP3P level and hence the distortion energy of the solvent mole-

TABLE III. Dipole Moments and Energies of Liquid Water for Partially Coupled Model.

	B1	B2	B3	B4	B4-PTE
μ	2.3	3.50	2.71	2.73	2.73
$\Delta\mu$	0.35	0.53	0.75	0.73	0.73
E^{int}	-20.36	-25.9	-33.6	-34.7	-34.7
E^{pol}	1.35	2.3	3.6	3.7	5.0
E^{LJ}	2.01	3.9	5.7	5.8	5.8
$\langle E \rangle$	-8.5	-9.9	-12.1	-12.5	-11.9

Dipoles are in debyes; energies are in kilocalories per mole. The internal energy $\langle E \rangle$ was calculated as $\frac{1}{2}(E^{\text{int}} + E^{\text{pol}} + E^{\text{LJ}})$. For a description kilocalories per moles basis sets B1, B2, B3, and B4 see the text.

TABLE IV.
Dipole Moments and Energies of Liquid Water for Completely Coupled Model.

	B1	B2	B3	B4	B4-PTE	B4-PTDE
μ	2.28	2.53	2.71	2.75	2.75	2.68
$\Delta\mu$	0.33	0.56	0.75	0.75	0.75	0.81
E^{int}	-19.7	-28.1	-36.9	-38.0	-38.0	-35.1
E^{pol}	1.25	2.5	3.9	4.2	5.7	4.4
E^{LJ}	1.96	4.3	6.7	6.6	6.6	6.8
$\langle E \rangle$	-7.6	-9.3	-10.8	-11.4	-10.1	-9.7

Dipoles are in debyes; energies are in kilocalories per mole. The internal energy $\langle E \rangle$ was calculated as $\frac{1}{2}(E^{\text{int}} + E^{\text{LJ}}) + E^{\text{pol}}$. For a description of basis sets B1, B2, B3, and B4 see the text.

cules is not included whereas this energy is properly taken into account by the CC method. The values given in Tables III and IV were calculated at the HF level. For B4 we also give the results obtained when the MP2 corrections were included: the PTE and PTDE calculations. In general and independent of the version used, PC or CC, at the HF level the energy is overestimated. The consideration of the correlation energy decreases the energy and brings the calculated value (10.1 kcal/mol) close to the experimental²⁶ one (9.92 kcal/mol). This effect can be completely assigned to the larger value of the distortion energy when calculated at the MP2 level. The lowering of the energy is even larger in PTDE calculations (9.7 kcal/mol): in this case, to the effect indicated above we must add the lowering of the dipole moment shown in Table IV that results in the lowering of the interaction energy. This trend of decreasing solvation energies when electron correlation is included confirms the results obtained in previous studies in the context of the continuum model.

The results obtained with the B2 and B4 basis sets for the oxygen–oxygen radial distribution function using the PC and CC versions are shown in Figures 5 and 6, respectively, and are compared with experimental data. The solvent structure is well represented by the PC method. With the B4 basis set the first peak is shifted by less than 0.1 Å inward and is increased by 0.25 units in height. This trend is in agreement with the results obtained with a polarizable model by Ahlström et al.^{14d} using molecular polarizabilities. It is remarkable that the second peak is also very well reproduced, which is not the case when the TIP3P model is used. The results obtained with the CC version are displayed in Figure 6. For B4 the height of the first peak is overestimated by 0.8 units and the O–O separation is too short at 2.7 Å. The second peak exhibits os-

cillations that are too large. The solvent structure is overestimated. Similar behavior was found by Tu and Laaksonen^{4d} in an HF/MM study. The B2 basis set provides better results; in fact, it almost reproduces the experimental values. Given that B2 underestimates the induced dipole moment and internal energies while B4 yields values for these magnitudes close to the experimental values, we conclude that our procedure overestimates the solvent structure. This defect is probably due to the use of fixed charges in the MD calculations. Indeed, it is well known that simulations performed with fixed-charge models yield overstructured solvents when

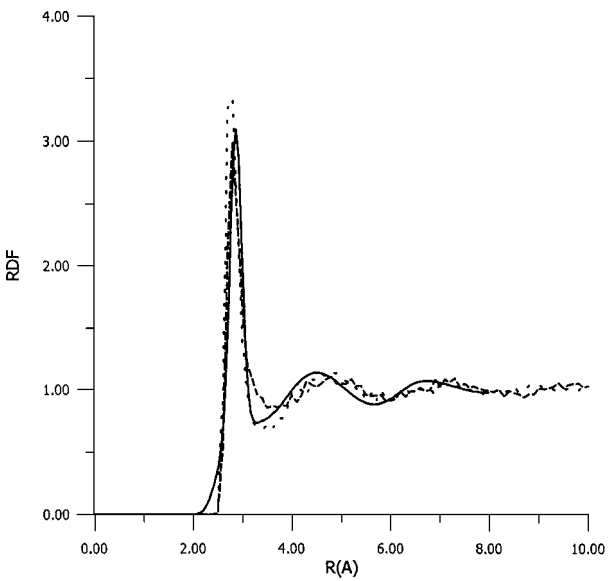


FIGURE 5. The O (solute)–O (solvent) radial distribution function of water obtained with the partially coupled method. (---) The results from B2, (···) the results from B4, and (—) the experimental results from ref. 29.

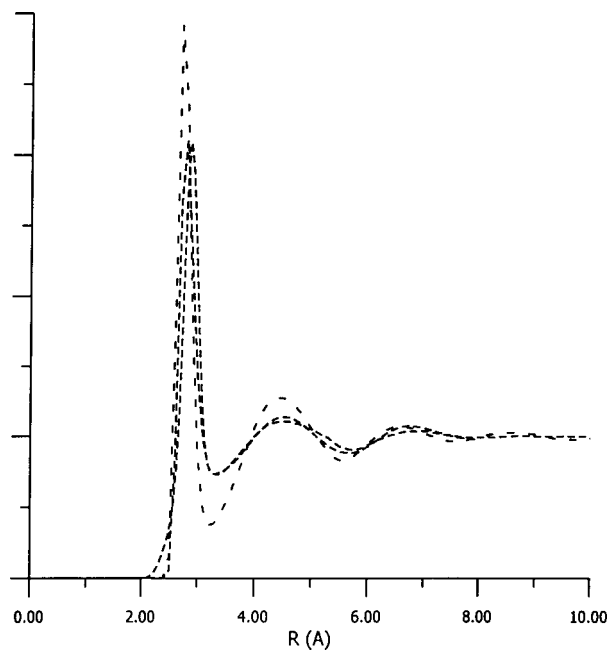


FIGURE 6. The O (solute)–O (solvent) radial distribution function of water obtained with the completely coupled method. (---) The results from B2, (· · ·) the results from B4, and (—) the experimental results from ref. 29.

compared with polarizable calculations for the same final value of the in-solution dipole moment.^{14d}

METHANOL

Here we present preliminary results for the methanol liquid system. The basis set used was B4, which, as is the case for water, provides values for the *in vacuo* dipole moment and polarizability close to the experimental values. The field force parameters used in the MD calculation were the OPLS values from Jorgensen.²⁷ This system is characterized by a high degree of short-range structure. However, the number of hydrogen bonds formed is less than in water, being about two bonds per molecule. As a consequence, the induced dipole value (close to 0.5 D) is less than that obtained for water, despite the methanol polarizability being greater. The in-solution dipole moment obtained with the PC version is 2.4 D, which is slightly larger than the OPLS value (2.2 D). The height of the first peak of the oxygen–oxygen radial distribution function, $g_{OO}(r)$ (see Fig. 7) is consequently higher than the OPLS function. Nevertheless, the behavior of the thermodynamics and structural properties is satisfactory. For instance, the first maximum of $g_{OO}(r)$ appears at 2.8 Å, which is also the experimental

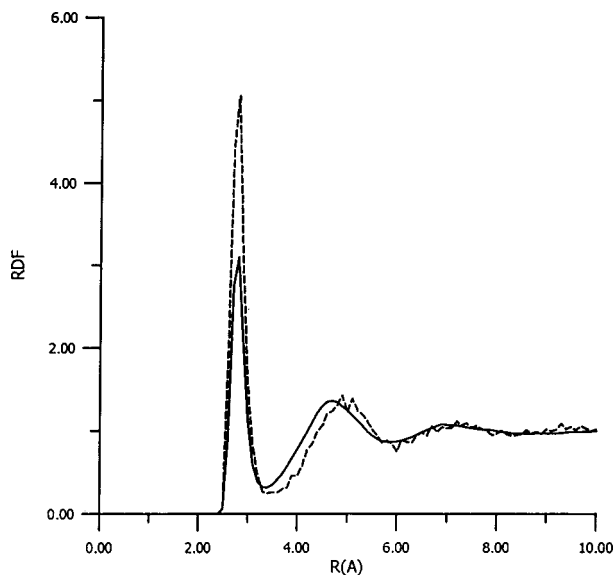


FIGURE 7. The O (solute)–O (solvent) radial distribution function of methanol. (---) The results from the partially coupled method, and (—) the OPLS results from ref. 27.

value. The averaged total potential energy calculated at the MP2E level was 8.6 kcal/mol, which also coincides with the experimental value. Similar to the study of the liquid water system, the inclusion of the corrections due to the electron correlation shows itself to be fundamental for a correct description of the internal energy.

Conclusions

The correct description of the charge distribution of molecules in solution is important because it determines the solute's reactivity, its spectroscopic properties, the nature and magnitude of its interactions with other molecules, etc. It is not easy to obtain a satisfactory solution to this problem because the polarization of solute molecules in liquid environments results from the interplay of such diverse factors as inclusion of the mutual polarization between the solute and solvent molecules, the proper description of the solute polarizability, the inclusion of the effect of the electron exchange component, and an adequate description of the solvent structure. In this article we proposed two versions of a mean field theory that permit the direct calculation of the solvent effect by combining QM and MD simulations and that include almost all the factors indicated above. We showed that when used with a basis set of high quality and whenever we include

the electron correlation, the two versions (PC and CC) of the method provide values for the dipole moment, internal energy, and radial distribution function that compare well with the experimental values and with the results obtained by other workers. Further improvements to the proposed method will come from the use of improved LJ parameters or taking into consideration the restriction that Pauli's principle imposes on the free displacement of the solute charge distribution as a response to the electric fields generated by the solvent molecules. From a computational point of view, this effect could be approximated through the introduction of explicit terms²⁸ into the molecular Hamiltonian or the use of pseudopotentials^{4a} or density functionals.^{3c, 3d}

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- Very good fits can be obtained with a reduced number of charges. For instance, in the water-water system, only 60 charges arranged around the solute molecule on spherical shells are enough to adequately reproduce the value of the averaged solvent electrostatic potential generated by 1000 solvent configurations. Several test calculations performed to determine how the position of the charges affects the quality of the fit showed that values between 2 and 3 Å for the radius of the first shell provide fits that differ by less than 0.1 kcal/mol.
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